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Epidemiology: Comparison of Multiple Studies or Literature Review

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EXECUTIVE SUMMARY

Tracked Safety Issue 1355 concerns the effects of prenatal exposure to acetaminophen. This review summarizes the epidemiologic data on urogenital abnormalities associated with prenatal acetaminophen exposure. In brief, one study found an association with reduced penile width, one study found a decrease in mean anogenital distance, three studies found associations with cryptorchidism, and three studies found no associations. All studies included adjustments for relevant covariates, though of course residual confounding is always a possibility. Biological plausibility is suggested by toxicologic data indicating that acetaminophen can act as an endocrine disrupter. Some evidence suggests that other analgesics have stronger associations with urogenital defects than acetaminophen.

While acetaminophen remains the preferred analgesic during pregnancy (due to the known risks of alternative analgesics), these findings, like the data on neurodevelopmental outcomes, suggest that its use during pregnancy is not necessarily completely benign for the fetus (except when it is used as an antipyretic, which some data indicate may be protective). It would be desirable for the agency to communicate this message to healthcare providers and pregnant women, considering that acetaminophen is so commonly used by women during their pregnancies, and that many perceive acetaminophen to be risk-free.

Additionally, it is noted that the description of the National Birth Defects Prevention Study in the current Ofirmev (intravenous acetaminophen) label is incorrect.

1 INTRODUCTION

Tracked Safety Issue (TSI) 1355 concerns the effects of prenatal exposure to acetaminophen. Originally the focus of the TSI review was on neurodevelopmental outcomes in prenatally exposed children. This topic was the subject of a Medical Policy and Program Review Council (MPPRC) meeting held on January 24, 2018, and was also discussed during the EMA/FDA Pharmacovigilance cluster conference call on February 28, 2018; although the MPPRC meeting focused only on neurodevelopmental outcomes, the topic of urogenital abnormalities associated with prenatal acetaminophen exposure was discussed during the call with the EMA.

A recent systematic review and meta-analysis of studies of analgesic use during pregnancy reported a combined odds ratio of 1.11, 95% CI: 1.00–1.23 for cryptorchidism,[1] but this meta-analysis included studies that did not distinguish among different analgesics, whereas the focus of this review will be on urogenital anomalies associated with prenatal acetaminophen exposure.

Accordingly, the purpose of this review is to summarize and evaluate the available epidemiologic data on the association of urogenital abnormalities with in utero acetaminophen exposure.

2 REVIEW METHODS AND MATERIALS

Relevant epidemiological studies of urogenital outcomes following in utero exposure to acetaminophen were identified by consulting the recent EMA Signal Assessment Report

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dated 8 February 2018 on prenatal exposure to acetaminophen, and the aforementioned systematic review by Gurney et al. In addition to references obtained from these sources, PubMed was searched to identify any additional relevant publications. A PubMed search on 7/2/2018 for the terms "acetaminophen pregnancy urogenital" returned 39 references. Of these, 16 reported nonclinical data, 3 were letters, 3 were review articles, and 15 were irrelevant to the topic of pregnancy exposure and urogenital outcomes, and thus were excluded. The 2 relevant articles[3,7] had already been identified from previous sources. Studies that analyzed a combined exposure (acetaminophen plus other analgesics) were not included.

3 REVIEW RESULTS

The following is a summary of the 8 relevant epidemiological studies identified as described above. A table in the appendix to this review provides descriptions of each study.

3.1 FELDKAMP ET AL. 2010[2]

This study evaluated data from the National Birth Defects Prevention Study (NBDPS), a ten-site surveillance study of selected birth defects, with controls selected randomly from among live births at each site; births between October 1, 1997 and January 1, 2005 comprised the sample. Cases of birth defects included in the sample were reviewed by clinical geneticists, and telephone interviews were conducted of mothers of cases and controls to determine prenatal medication exposure and other clinical details of the pregnancy. Exposure to acetaminophen was defined as use between the last menstrual period and week 12 of pregnancy. The sample included 11,610 birth defect cases and 4,500 controls. First trimester exposure to acetaminophen was reported in 47% of cases and 46% of controls overall. Overall, after adjustment for relevant covariates, none of the approximately 50 types of birth defects analyzed in the study showed an association with acetaminophen exposure; the only urogenital defect analyzed was hypospadias, which had an adjusted odds ratio of 0.9 (95% CI 0.7-1.1). Furthermore, among mothers with both a first trimester fever and infection, use of acetaminophen significantly decreased risks of the following defects (listed with aOR and 95% CI): anencephaly/craniorachischisis (0.35, 0.08–0.80), encephalocele (0.17, 0.03–0.87), anotia/microtia (0.25, 0.07–0.86), cleft lip (0.44, 0.26–0.75), gastroschisis (0.41, 0.18–0.94). The authors concluded that acetaminophen exposure in the first trimester was not associated with birth defects, but that first trimester use in the setting of fever and infection appeared to be protective.

3.2 FISHER ET AL. 2016[3]

The Cambridge Baby Growth Study is a U.K. prospective cohort study of mothers and their infants, with recruitment at the pregnancy week 12 of ultrasound. For this analysis of anogenital distance, penile length, and testicular descent, the sample included 676 mothers and 681 male infants. Physical examinations of the infants were conducted periodically from birth through 2 years of age. Maternal drug exposure was determined by questionnaire (handed out to mothers at the time of recruitment and completed by them after delivery). Acetaminophen exposure during gestational weeks 8-14 was

associated with a 0.27-standard deviation level of shortened anogenital distance (p=0.014), with no difference associated with exposure before or after 8-14 weeks, and no associations with penis length, cryptorchidism, or measured testicular descent distance.

3.3 INTERRANTE ET AL. 2017[4]

This study also analyzed NBDPS data and was conducted with collaboration from FDA (James Trinidad and Lockwood Taylor from DEPI were co-authors of the paper). Please refer to the above description of the Feldkamp article (in Section 3.1) for details regarding the NBDPS. In this study, first trimester exposure to nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids was analyzed with exposure to acetaminophen as the reference group, in a total of 9179 offspring with birth defects and 5944 controls with prenatal exposure to one of the analgesics of interest. Accordingly, this study provides comparative risk data (comparing NSAID and opioid exposure to acetaminophen exposure). Hypospadias was the only urogenital defect analyzed; for hypospadias the adjusted ORs vs acetaminophen were for NSAIDs, 1.3 (95% CI 1.1-1.5); for opioids, 1.0 (95% CI 0.6-1.8); and for NSAIDs+opioids, 1.0 (95% CI 0.6-1.6). Thus, acetaminophen had a lower risk than NSAIDs, but of course there was no measurement of the risk in offspring unexposed to analgesics.

3.4 JENSEN ET AL. 2010[5]

This study used data from the Danish National Birth Cohort to assess the relationship of prenatal acetaminophen, ibuprofen, and aspirin exposure with cryptorchidism. The sample was 47,400 live born male infants, followed until the ages of 6-13 years for outcome codes indicating cryptorchidism or orchiopexy in the Danish National Patient Registry. Maternal use of analgesics was determined from maternal telephone interviews conducted at pregnancy weeks 17 and 32, and postpartum. The strongest association for cryptorchidism by timing of acetaminophen exposure was found for exposure during both the first and second trimester, with an adjusted hazard ratio of 1.33 (95% CI 1.00-1.77); there were no significant associations with orchiopexy.

3.5 KRISTENSEN ET AL. 2010[6]

This prospective cohort study of 1499 Finnish infant boys and 1071 Danish infant boys, mothers completed a questionnaire administered in the third trimester regarding medication use during pregnancy; the male infants were examined at birth for congenital cryptorchidism. Use of acetaminophen during the second trimester showed a nearly statistically significant risk (adjusted OR 1.97, 95% CI 0.94-4.12), use during the first trimester showed an adjusted OR of 1.61, 95% CI 0.66-3.90; there were stronger associations with second trimester exposure to ibuprofen (adjusted OR 4.59, 95% CI 1.1-19) and aspirin (adjusted OR 3.76, 95% CI 1.15-12.3). Also, from a figure in the publication, exposure for 2+ weeks to acetaminophen during the first two trimesters was associated with a prevalence of cryptorchidism at birth of approximately 17% (p-value versus no analgesics >0.05, adjusted for adjusted for disease, use of other medicine and gestational age, an odds ratio was not provided).

3.6 LIND ET AL. 2017[7]

The Odense Child Cohort prospective cohort study in Southern Denmark enrolled pregnant women during the period 2010-2012. Mothers reported use of medication during pregnancy via a questionnaire sent to them at gestational age 10-27 weeks, and again via a second questionnaire at gestational week 28. Exposure was defined as use at least once during the period of interest. Exposure timing was classified as during first trimester, second trimester, both first and second trimester, or unknown (but during the first 28 weeks). For this study 470 infant girls and 557 infant boys were examined at 3 months of age to determine anogenital distance and penile width. There were no significant findings regarding anogenital distance and prenatal acetaminophen exposure in males or females; there was a significant reduction in mean penile width of 0.7 mm with exposure "at unknown time" during the first 28 weeks but not with other categories of acetaminophen exposure. Prenatal exposure to both acetaminophen and other analgesics was associated with significant mean reduction of 4.1 mm in anogenital distance in males, however.

3.7 REBORDOSA ET AL. 2008[8]

As with the previously described study by Jensen and colleagues, this study employed the Danish National Birth Cohort to evaluate the risk of a variety of congenital defects with prenatal exposure to acetaminophen in a sample of 88,142 live born infants, 26,424 of whom had first trimester exposure to acetaminophen. The authors reported no increase in overall defects or specific categories of defects with prenatal acetaminophen exposure. With respect to urogenital abnormalities, adjusted HRs for first trimester acetaminophen exposure were, for hypospadias, 1.0 (0.8-1.3); and for undescended testis, 1.2 (0.8-1.9).

3.8 SNIJDER ET AL. 2012[9]

The Generation R study prospectively enrolled pregnant women in the region of Rotterdam, the Netherlands, during 2002-2006. Medication exposure was determined by questionnaires at gestational weeks 12, 20, and 30. Cryptorchidism and hypospadias were assessed during preventative health care visits through age 36 months. The sample for this analysis was 3184 boys. For cryptorchidism, the adjusted OR was 1.89 with 95% CI 1.01–3.51 for acetaminophen exposure in the second trimester (there was a stronger association with other painkillers, defined as "all other painkillers, including NSAIDs and aspirin, on prescription or over-the counter"). No significant associations were found for acetaminophen exposure in the first or third trimester, and there were no associations with hypospadias.

4 DISCUSSION

The following table summarizes the main results of these studies of urogenital outcomes with intrauterine acetaminophen exposure. Statistically significant associations with acetaminophen are bolded.

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Study	Data source	Outcome	Risk estimate for prenatal APAP exposure versus unexposed
Feldkamp 2010	National Birth Defects Prevention Study	Hypospadias	Adjusted OR 0.9 (0.7-1.1) for first trimester exposure overall; in subgroup of women with fever and infection, 0.42 (0.17-1.00)
Fisher 2016	Cambridge Baby Growth Study	Anogenital distance	**Exposure during wks 8-14 associated with -0.27 SD reduction in anogenital distance (p=0.014).** No association with exposure before or after wks 8-14
Interrante 2017	National Birth Defects Prevention Study	Hypospadias	**Adjusted OR for NSAIDs vs acetaminophen = 1.3 (1.1-1.5).** Acetaminophen vs. no exposure not analyzed
Jensen 2010	Danish National Birth Cohort	Cryptorchidism or orchiopexy	**Cryptorchidism: for exposure in both 1st and 2nd trimester, adjusted HR 1.33 (1.00-1.77). No associations with orchiopexy.**
Kristensen 2010	Univ. Hosp. of Copenhagen	Cryptorchidism	Adjusted OR for cryptorchidism with acetaminophen use in 2nd trimester 1.97 (0.94–4.12). **2+ weeks acetaminophen use during first two trimesters significantly increased cryptorchidism (OR not shown)**
Lind 2017	Odense Child Cohort, Denmark	Anogenital distance, penile width	**Penile width reduced 0.7 (0.3, 1.1) mm with exposure at "unknown time" during first 28 weeks**, otherwise no associations
Rebordosa 2008	Danish National Birth Cohort	Hypospadias and cryptorchidism	Hypospadias-- adjusted OR 1.01 (0.76-1.33) Cryptorchidism—adjusted OR 1.24 (0.79-1.94)
Snijder 2012	Generation R Study, the Netherlands	Hypospadias and cryptorchidism	**For cryptorchidism, adjusted OR 1.89; 95% CI 1.01-3.51, with acetaminophen exposure during wk 14-22**,not earlier or later exposure. No associations w/hypospadias

In summary, for prenatal acetaminophen exposure, one study (Interrante) found an association with hypospadias, one study (Fisher) found a decrease in mean anogenital distance, one study (Lind) found reduced penile width, and three studies (Jensen, Kristensen, Snijder) found associations with cryptorchidism. Relative risk estimates were below two. All studies included adjustments for relevant covariates, though of course residual confounding is always a possibility.

The strengths and weaknesses of these studies should be borne in mind when evaluating their inferential value. One limitation of the National Birth Defects Prevention Study (Feldkamp et al. and Interrante et al.) is that mothers reported on drug exposure post-delivery, at a time when the outcomes may have been known, which could introduce recall bias (to the extent that a mother whose child has a known birth defect may make a point of remembering pregnancy drug exposures). This could bias the results towards an association. However, the Feldkamp study did not find an association with hypospadias, and the Interrante study did not have an unexposed reference group. The Jensen study assessed exposure from week 32 until delivery, postnatally, but found no association with third trimester exposure. The Fisher study found an association with reduced anogenital distance using acetaminophen exposure data obtained post-delivery, but it seems unlikely

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that anthropometric measurement of anogenital distance would influence maternal recall of acetaminophen use. The other studies collected data on exposure before the outcome was known. Overall, for those studies which did find an association with maternal acetaminophen use, it does not appear that recall bias would be a plausible explanation for the reported association.

Another limitation of these studies is of course the possibility of confounding, given the observational nature of the data. However, all studies reviewed adjusted for covariates in an attempt to account for confounding factors, though the specific covariates varied across studies. First, we should consider what the established risk factors are for these outcomes.

Unfortunately, risk factors for reduced anogenital distance are not well characterized.[7] For hypospadias, a recent review of known or suspected risk factors noted genetics/family history, maternal factors such as age, hypertension, thyroid disease, diabetes, BMI, white race education level, use of progestins, parity, and pesticide exposure, as well as geographic variations.[10] Possible risk factors for cryptorchidism are believed to include prematurity, low birth weight, and endocrine disruptor exposure.[11]

For each study, in the appendix table, the covariates analyzed as possible confounders are shown in bold type. To gain a better understanding of the role that confounding may have played in these studies, it is particularly important to examine how potential confounders were analyzed in the studies that identified an association with maternal acetaminophen use. The Fisher et al. study of anogenital distance, which found an association with maternal use during weeks 8-14, adjusted for body weight and acetaminophen use during other time periods, but other covariates tested in the model were not significant (age, deprivation index, body mass index, blood glucose, parity, smoking, type of delivery and ethnicity). Similarly, the study by Lind and colleagues that reported an association of maternal acetaminophen use and reduced penile width adjusted for age and weight at 3 months, but other covariates (parity, smoking, fertility treatment, BMI, ethnicity, education) were not significant in the outcome model. Among the studies that found an association with cryptorchidism, the impact of covariate adjustment also was modest. In the Snijder et al. study, the unadjusted OR for cryptorchidism was 1.85, while the OR adjusted for maternal age, education, body mass index, general health, use of co-medication, underlying diseases, and fever was similar, at 1.89. Similarly, in the study by Jensen et al., the unadjusted OR for cryptorchidism was 1.33, while the OR adjusted for age, occupation, parity, time to pregnancy, smoking, and infertility treatment was also 1.33. The study by Kristensen et al. adjusted for indication, use of other medication, gestational age, and twins (other covariates were not significant in their model), and found a near-significant adjusted OR of 1.97 and an unadjusted OR of 1.93.

Overall, the studies that reported some association identified few specific covariates with a material impact on the risk for these urogenital outcomes. This may reflect the challenges of defining risk factors for these outcomes. Although reasonably thorough efforts were made to adjust for possible confounders in every study, because the risk

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factors for urogenital defects are not known with certainty, there is still the possibility of residual confounding.

Confounding by indication in particular could be an important issue if the condition that led the mothers to take acetaminophen was itself associated with a higher risk of urogenital defects. The Feldkamp and Kristensen studies adjusted for indications reported during the pregnancy, and the Feldkamp study showed a reduction in the risk of hypospadias in the setting of fever and infection that almost reached statistical significance, suggesting a protective effect; however, Rebordosa and colleagues reported that adjustment for indication had no significant impact. The Interrante study controlled for indication to the extent that it compared hypospadias risks by type of analgesic, so that all mothers had required some type of analgesic.

To gain insight with respect to the adjustment for other risk factors, one can compare the adjusted to the unadjusted risks in articles that presented both. On balance, across studies, adjustments for possible confounders or risk factors had little impact on the risk estimates reported. The Jensen study found that adjustment for age, occupation, parity, time to pregnancy, infertility treatment and smoking had essentially no impact on the acetaminophen hazard ratio. Similarly, in the Kristensen study of cryptorchidism, adjustment for gestational age, maternal diseases and concomitant medication did not materially affect the risk estimate for cryptorchidism, and in the Snijder study, adjustment for maternal age, education, BMI, general health, concomitant medications, diseases and fever did not affect the risk estimate very much. Finally, in the Rebordosa study, the risk estimates for both cryptorchidism and hypospadias after adjustment for maternal age, birth year, birth order, gender, and chronic diseases were very similar to the unadjusted risk estimates. In the Lind study, none of the covariates tested had a measurable influence on anogenital distance. On balance, the covariates adjusted for in these studies did not seem to have much influence on the risk estimates, which may reflect the difficulty defining risk factors for these outcomes.

A relative strength of all the studies is that the outcome in all cases was determined by physical examination, which should provide good specificity. However, the relative infrequency of the outcomes of hypospadias and cryptorchidism presents challenges in terms of the statistical power of the studies, as larger sample sizes are needed for meaningful statistical estimates of risk. This does not apply to anogenital distance or penile width measurements, which are provided for each subject. On balance, the studies were generally well-conducted although they share the generic limitations that apply to observational data.

Regarding the clinical significance of these findings, cryptorchidism and hypospadias require surgical correction, and additionally cryptorchidism is a risk factor for testicular cancer even after surgery.[12] With respect to reduced anogenital distance, this has been associated with lower semen quality, though clinical utility of this parameter is not well defined.[13]

The Feldkamp study is described (incorrectly) in the Ofirmev (intravenous acetaminophen) label, as follows: “A population-based, case-control study from the

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National Birth Defects Prevention Study showed that 11,610 children with prenatal exposure to acetaminophen during the first trimester had no increased risk of major birth defects compared to 4,500 children in the control group." As this was a case-control study, it would be more appropriately described as including 11,610 cases of birth defects and 4,500 control children, with prenatal exposure to acetaminophen compared between the two groups. Although the study did not find an increased risk of birth defects, an important component of the results was that among mothers with first trimester fever and infection, use of acetaminophen significantly decreased risks of several defects (see above). A revised description of the study might therefore be: "A population-based, case-control study of 11,610 children with birth defects and 4,500 children without birth defects found no increased risk of major birth defects with first trimester prenatal exposure to acetaminophen; furthermore, first trimester use of acetaminophen by mothers with fever and infection appeared to reduce the risk for several types of birth defects." In fact, the Feldkamp study showed a reduction in the risk of hypospadias in the setting of fever and infection that almost reached statistical significance. Parenthetically, a protective effect of antipyretics in the setting of maternal fever was also noted in some of the data on neurodevelopmental outcomes,[14,15] as discussed in the DEPI-I review of that topic completed October 14, 2016.[16] Treatment of maternal fever >39.5 degrees has been recommended to reduce the risk of spontaneous abortion, prematurity, and central nervous system defects.[17]

With respect to biological plausibility, the constellation of cryptorchidism, hypospadias, poor semen quality and testicular cancer has been termed testicular dysgenesis syndrome by some investigators, and is believed to result from abnormal in utero development.[18] Furthermore, acetaminophen crosses the placenta[19] and has shown endocrine disrupting properties in various models.[20,21]

It has been hypothesized that cryptorchidism, hypospadias, reduced fertility and reduced anogenital distance may result from androgen insufficiency during gestational weeks 8-14;[6] this time period has been referred to as the male programming window[5] though actual testicular descent occurs in the third trimester, and some data indicate that for hypospadias, the critical developmental window is 8-20 weeks of gestation.[22]

These considerations add to the complexity of establishing a risk window for analyzing in utero exposure, and may possibly explain the absence of associations in some of the studies reviewed. If weeks 8-14 are the critical time for development, then simply analyzing exposure by trimester might not be sufficient, as the critical time would span the end of the first trimester and the beginning of the second trimester, while exposure very early in the first trimester or late in the second trimester may not affect urogenital development. We note that the Feldkamp and Rebordosa studies, neither of which identified an association, analyzed only first trimester exposure. On the other hand, Fisher and colleagues found a reduction in anogenital distance with exposure at 8-14 weeks, but not earlier or later, and Jensen et al. reported an association with cryptorchidism when exposure occurred during both trimesters 1 and 2, but not for exposure in either separately. Snijder et al. reported an association with cryptorchidism

for exposure during week 14-22, but not earlier or later. Overall, no study that evaluated first trimester exposure alone found an association with urogenital outcomes.

5 CONCLUSIONS

The available epidemiologic data suggest an association between prenatal acetaminophen exposure and urogenital defects; while some studies had negative findings, that might have resulted from including exposure times of low relevance; i.e., early first trimester. Although causality cannot be proven per se from observational data alone due to the possibility of confounding, the findings should be interpreted in the context of toxicologic data indicating acetaminophen can exert endocrine effects. Some evidence suggests that other analgesics have stronger associations with urogenital defects than acetaminophen.

6 RECOMMENDATIONS

While acetaminophen remains the preferred analgesic during pregnancy (due to the known risks of alternative analgesics), these findings, like the data on neurodevelopmental outcomes, suggest that its use during pregnancy is not necessarily free of risk to the fetus (excepting use an antipyretic, which some data indicate may be protective). It would be desirable for the agency to communicate this message to healthcare providers and pregnant women, considering that acetaminophen is so commonly used by pregnant women, some of whom may perceive acetaminophen to be risk-free (for example, the parents.com website says, "Follow the dosage on the bottle--you'll be okay taking Tylenol while pregnant."[23]) The somewhat more nuanced message to convey to pregnant women would be of this nature: acetaminophen is the safest pain reliever during pregnancy and should be used as needed to reduce fever, but heavy use for other reasons may have risks, so pregnant women should be careful about casual use of acetaminophen when it is not strongly needed for pain or other purposes.

In addition, the description of the Feldkamp study in the Ofirmev label should be revised.

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APPENDIX TABLE. Studies of urogenital outcomes following in utero acetaminophen exposure

Abbreviations: ASA, aspirin; HR, hazard ratio; IRR, incidence rate ratio; OR, odds ratio; RR, risk ratio; SD, standard deviation

Study	Objectives/Aims/ Scope	Design	Data Source	Subject selection criteria	Exposure	Outcome(s)	Sample Size	Statistical Analyses with covariates included in bold	Study Results (significant results in bold)
Feldkamp 2010	To investigate if 1st trimester exposure to acetaminophen increases major birth defects	Case-control	National Birth Defects Prevention Study, 1997-2004	Cases of birth defects reported by participating sites. Those with chromosomal & genetic etiologies excluded. Control infants selected randomly by each site.	Maternal interview within 24 mos of delivery to determine use of acetaminophen during 1st trimester; mothers who used combination products excluded	Hypospadias	Overall, 11,610 cases & 4,500 controls. For hypo-spadias, 758 cases, 2094 controls	Logistic regression adjusted for **maternal age, education, BMI, gestational diabetes, smoking, folic acid use, parity & ethnicity; stratified by infection and fever.**	Adjusted OR 0.9 (0.7-1.1); in subgroup of women with fever and infection, 0.42 (0.17-1.00), and in women without fever or infection, 0.83 (0.65-1.06) This study is described (incorrectly) in the Ofirmev label, as follows: "A population-based, case-control study from the National Birth Defects Prevention Study showed that 11,610 children with prenatal exposure to acetaminophen during the first trimester had no increased risk of major birth defects compared to 4,500 children in the control group."

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Study	Objectives/Aims/ Scope	Design	Data Source	Subject selection criteria	Exposure	Outcome(s)	Sample Size	Statistical Analyses with covariates included in bold	Study Results (significant results in bold)
Fisher 2016	To investigate the association between maternal acetaminophen use and male infant genital outcomes	Prospective cohort study	Cambridge Baby Growth Study, Apr 2001-Mar 2009	Mothers aged 16+ years were recruited at the time of pregnancy week 12 ultrasounds, Addenbrooke's Hospital, Cambridge	Maternal questionnaires recording acetaminophen use were completed after delivery; timing <8 wks, 8-14 wks, or >14 wks	Infants examined up to age 24 mos for anogenital distance, penis length, testicular descent	408 male offspring who had ano-genital distance mea-sured & timing of APAP use reported	Repeated outcome measures analyzed with linear mixed models. Analyses adjusted for **child's weight & acetaminophen exposure during other gestational periods**, but maternal covariates (**age, geographic socioeconomic status (as measured by UK deprivation index), BMI, fasting glucose, parity, smoking, method of delivery, ethnicity**) were not significant in the model	**Exposure during wks 8-14 associated with -0.27 SD reduction in anogenital distance (p=0.014); no association with exposure before or after 8-14 wks.** No association with penis length, cryptorchidism or testicular descent distance.
Interrante 2017	To assess the risk of birth defects with prenatal exposure to NSAIDs & opioids vs. acetaminophen	Case-control	National Birth Defects Prevention Study, 1997-2011	Cases of birth defects reported by participating sites. Those with chromosomal & genetic etiologies excluded. Control infants selected randomly by each site.	Maternal interview within 24 mos of delivery to determine exposure one month preconception to 3rd month of pregnancy	Hypospadias	1384 cases, 5944 controls	Logistic regression to calculate OR (adjusted for **maternal age, ethnicity, parity, education, alcohol, smoking, antibiotic use, location, calendar year of delivery)**, for risk with NSAIDs, opioids, and both in combination, with acetaminophen exposure as reference	**Adjusted ORs vs acetaminophen: for NSAIDs = 1.3 (1.1-1.5);** for opioids, 1.0 (0.6-1.8); for NSAIDs+opioids 1.0 (0.6-1.6)

Study	Objectives/Aims/ Scope	Design	Data Source	Subject selection criteria	Exposure	Outcome(s)	Sample Size	Statistical Analyses with covariates included in bold	Study Results (significant results in bold)
Jensen 2010	To determine the association of prenatal exposure to acetaminophen, ibuprofen and ASA with cryptorchidism	Prospective cohort study	Danish National Birth Cohort, 1996-2002	Danish mothers recruited at first prenatal visit	Ascertained from maternal telephone interviews pre-delivery, week 17 & 32, and post-delivery for third trimester exposure	ICD 10 diagnosis of cryptorchidism, or code for orchiopexy procedure, in Danish National Patient Registry	47,400 male infants followed up for at least 6 yrs	Cox regression, adjusted for **maternal age, occupational status, parity, time to pregnancy, smoking, infertility treatment**	**Cryptorchidism: for exposure in both 1st and 2nd trimester, adjusted HR 1.33 (1.00-1.77).** Unadjusted HR also 1.33**.** No associations with orchiopexy. No associations w/ibuprofen, ASA
Kristensen 2010	To investigate whether mild analgesic exposure in utero manifests as male reproductive disorders	Prospective birth cohort study	University Hosp. of Copenhagen (1997-2001) & Turku Univ. Central Hosp., Finland (1997-99)	Mothers recruited prenatally at either Danish or Finnish hospitals; had to be natives of that country	Questionnaires or interviews were administered in the 3rd trimester to ascertain exposure to acetaminophen, ibuprofen, ASA	Examination for cryptorchidism at birth	1499 Finnish infant boys and 1071 Danish infant boys	Logistic regression adjusted for **indication, use of other medication, gestational age, twins** per written questionnaire, (other covariates, i.e., **birthweight, twins per phone interview, maternal age, smoking, chronic disease, infectious disease**, were nonsignificant)	**Denmark: Adjusted OR for cryptorchidism with acetaminophen use in 2nd trimester 1.97 (0.94–4.12).** Unadjusted OR 1.93 (0.94-3.98) **Higher ORs for ASA, ibuprofen, multiple analgesics. Acetaminophen use for 2+ weeks during trimesters 1&2 significantly increased prevalence of cryptorchidism at birth (OR not shown).** Finnish data pooled all analgesics

Study	Objectives/Aims/ Scope	Design	Data Source	Subject selection criteria	Exposure	Outcome(s)	Sample Size	Statistical Analyses with covariates included in bold	Study Results (significant results in bold)
Lind 2017	To study the association of prenatal exposure to analgesics and anogenital distance	Prospective cohort study	Odense Child Cohort, Denmark, 2010-2012	Mothers recruited from among pregnant women in Odense, at time of routine prenatal ultrasound or first prenatal care visit	Determined exposure to acetaminophen, ASA & ibuprofen from two questionnaires, one after recruitment (10-27 wks), and a more specific questionnaire about OTC medication at wk 28	Anogenital distance, penile width measured at 3 mos of age.	470 girls, 557 boys	Multiple linear regression, adjusted for gestational **age and weight at 3 months**; other covariates (**parity, smoking, fertility treatment, BMI, ethnicity, education**) were not significant in model	No associations for girls. In boys, exposure to acetaminophen only showed no association with anogenital distance (but exposure to multiple analgesics shortened distance by mean of 4 mm). **Penile width reduced 0.7 (0.3, 1.1) mm with acetaminophen exposure at "unknown time" during first 28 weeks**
Rebor-dosa 2008	To determine if acetaminophen exposure during organogenesis is associated with congenital abnormalities	Prospective cohort study	Danish National Birth Cohort 1996-2003	Women were recruited at time of first prenatal visit. For inclusion in this study, women had to have provided information on 1st trimester acetaminophen use	Exposure determined from maternal questionnaires and telephone interviews pre-delivery	Congenital abnormalities identified from National Hospital Registry through 1/12/2006	88,142 mother-live singleton infant pairs	Cox proportional hazard analyses adjusted for **maternal age, birth year, birth order, gender, chronic diseases** such as diabetes, epilepsy, obesity, low fecundity. **Indication, fever, & pain** were not significant & were omitted from model	Adjusted HR for 1st trimester acetaminophen exposure: hypospadias, 1.0 (0.8-1.3); undescended testis 1.2 (0.8-1.9); crude HRs 1.02 and 1.21, respectively

Study	Objectives/Aims/ Scope	Design	Data Source	Subject selection criteria	Exposure	Outcome(s)	Sample Size	Statistical Analyses with covariates included in bold	Study Results (significant results in bold)
Snijder 2012	To examine the association between mild analgesic pregnancy exposures and cryptorchidism and hypospadia	Prospective cohort study	Generation R Study, the Netherlands, 2002-2006	Any pregnant woman in Rotterdam with due date Apr 2002-Jan 2006	Prenatal questionnaires completed in first, second, & third trimesters	Cryptorchidism and hypospadias diagnosed during clinical visits through age 4 yrs	3184 mother-boy pairs	Logistic regression adjusted for maternal age, education, BMI, general health, use of co-medication, underlying diseases, fever; these covariates were determined a priori, multiple other covariates were not significant. Reference group= women who used no medication during pregnancy	**For cryptorchidism, adjusted OR 1.89; 95% CI 1.01–3.51, with acetaminophen exposure during wk 14-22.** Unadjusted OR 1.85 (1.02-3.37). No associations in 1st or 3rd trimester. No associations w/hypospadias

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